

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

|   |                                  |
|---|----------------------------------|
| Inventor: Brown <i>et al.</i>   | Docket No: 383299-336US (107322) |
| Patent No.: 7,943,776   | Confirmation No.: 8437           |
| Issued: May 17, 2011  | Group Art Unit: 1625             |
| Serial No.: 10/581,305  | Examiner: COVINGTON, Raymond K   |
| Filed: October 12, 2006   |                                  |
| For: AMIDE DERIVATIVES BEARING A<br>CYCLOPROPYLAMINOACARBONYL<br>SUBSTITUENT USEFUL AS CYTOKINE<br>INHIBITORS |                                  |

**REQUEST FOR CERTIFICATE OF CORRECTION OF OFFICE MISTAKE  
UNDER 37 CFR § 1.322 AND APPLICANT MISTAKE UNDER 37 CFR § 1.323**

**Attn: Certificate Of Corrections Branch**

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

Sir:

Pursuant to the terms of 35 U.S.C. § 255 and 37 CFR §§ 1.322 and 1.323, Patentee requests that a Certificate of Correction be issued for the above-identified patent. The mistakes identified in the attached PTO/SB/44 (Rev. 04-05) Certificate of Correction comprise minor errors made in good faith by Patentee and errors made by the United States Patent and Trademark Office ("USPTO").

**USPTO Error**

Patentee requests that the following typographical errors be corrected as follows:

In column 53, claim 1, line 2, please change "allcyl" to --alkyl-- .

The correct text is shown in previously numbered Claim 1, corresponding to newly renumbered Claim 1 of the issued patent, of the Amendment filed on November 2, 2010, a copy of which is attached as Exhibit A.

In column 53, claim 5, line 38, please change "ylinethoxy" to --ylmethoxy--.

The correct text is shown in previously numbered Claim 9, corresponding to newly renumbered Claim 5 of the issued patent, of the Amendment filed on November 2, 2010 (Exhibit A).

In column 53, claim 5, line 44, please change "aminol" to --amino--.

The correct text is shown in previously numbered Claim 9, corresponding to newly renumbered Claim 5 of the issued patent, of the Amendment filed on November 2, 2010 (Exhibit A).

In column 53, claim 5, line 50, please change "benzoy" to --benzoyl--.

The correct text is shown in previously numbered Claim 9 corresponding to newly renumbered Claim 5 of the issued patent, of the Amendment filed on November 2, 2010 (Exhibit A).

In column 54, claim 5, line 4, please change "phenoxy" to --phenoxy--.

The correct text is shown in previously numbered Claim 9, corresponding to newly renumbered Claim 5 of the issued patent, of the Amendment filed on November 2, 2010 (Exhibit A).

#### **Patentee Error**

The following errors were made on the part of the Patentee. These errors are of minor character, are of a clerical or typographical error, and were made in good faith by Patentee. Patentee requests that the following typographical errors should be corrected as follows:

On the cover page, item (73) Assignee: "Asrazeneca AB, Sodertalje (SE)" should read as follows:

-- AstraZeneca AB, Sodertalje (SE) --

The correct text is shown for "Assignee" in "Assignment" of the Patent Assignment Abstract of Title for the above-identified patent, a copy of which is attached as Exhibit B.

The changes requested herein do not introduce new matter. Patentee also asserts that these changes would not require reexamination.

The fee specified at 37 C.F.R. §1.20(a) of **\$100** is being paid concurrently herewith via EFS-Web Fee Calculation Screen or accompanying Fee Transmittal. No fees beyond those specified in the EFS-Web Fee Calculation Screen (or accompanying Fee Transmittal) are believed to be due in connection with the submission of this paper. However, the Director is authorized to charge any fees that may required, or credit any overpayment, to Dechert LLP Deposit Account No. 50-2778 (Order No. 383299-336US (107322)).

Respectfully submitted,

Date: October 26, 2011

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**UNITED STATES PATENT AND TRADEMARK OFFICE  
CERTIFICATE OF CORRECTION**

Page 1 of 1

PATENT NO. : 7,943,776  
APPLICATION NO. : 10/581,305  
ISSUE DATE : May 17, 2011  
INVENTORS : Brown *et al.*

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below.

In column 53, claim 1, line 2, please change "allcyl" to --alkyl-- .

In column 53, claim 5, line 38, please change "ylinethoxy" to --ylmethoxy--.

In column 53, claim 5, line 44, please change "aminol" to --amino--.

In column 53, claim 5, line 50, please change "benzoy" to --benzoyl--.

In column 54, claim 5, line 4, please change "phenoxyl" to --phenoxy--.

On the cover page, item (73) Assignee, please change "Asrazeneca AB, Sodertalje (SE)" to  
-- Astrazeneca AB, Sodertalje (SE) --

**MAILING ADDRESS OF SENDER**

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# **Exhibit A**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

|             |  |                   |                       |
|-------------|--|-------------------|-----------------------|
| Applicant:  | Brown <i>et al.</i>  | Docket No:        | 383299-336US (107322) |
| Serial No.: | 10/581,305   | Confirmation No.: | 8437                  |
| Filed:      | October 12, 2006   | Group Art Unit:   | 1625                  |
| For:        | AMIDE DERIVATIVES BEARING A<br>CYCLOPROPYLAMINOACARBONYL<br>SUBSTITUENT USEFUL AS CYTOKINE<br>INHIBITORS | Examiner:         | COVINGTON, Raymond K  |

**RESPONSE AND AMENDMENT UNDER 37 CFR § 1.116**

**VIA EFS-WEB**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Applicant has considered the final Office Action mailed August 3, 2010 in the above-captioned application. Reconsideration of the claims in light of the amendments and remarks that follow is requested. This paper is being timely submitted within **three months** of the mailing date of the Office Action.

A Notice of Appeal is being filed concurrently herewith.

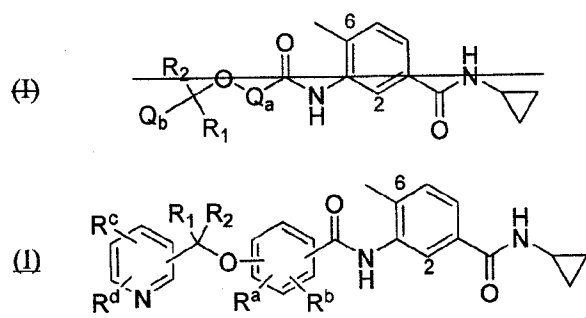
- **Amendments of the Claims** begin at **page 2** of this paper.
- **Remarks** begin on **page 7** of this paper.

## AMENDMENTS OF THE CLAIMS

The following **Listing of Claims**, in which deleted text appears as ~~struck through~~ or within bolded double brackets (e.g., **[[text]]**), and inserted text appears as underlined, will replace all prior versions and listings of claims in the application. Text within single brackets stems for the original claims and should not be deleted.

### Listing of Claims

**Claim 1** (currently amended): A compound of the according to structural Formula I



wherein:

Q<sub>a</sub> is phenyl, and Q<sub>a</sub> may optionally bear 1 or 2 substituents R<sup>a</sup> and R<sup>b</sup> are each, independently of one another, selected from the group consisting of hydrogen, hydroxy, halogeno, trifluoromethyl, cyano, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino and (1-6C)alkoxycarbonyl;

R<sub>1</sub> and R<sub>2</sub> are each independently of one another selected from the group consisting of hydrogen, (1-6C)alkyl, (2-6C)alkenyl and (2-6C)alkynyl; and

$Q_b$  is pyridyl, and  $Q_b$  may optionally bear 1 or 2 substituents  $R^c$  and  $R^d$  are each independently of one another, selected from the group consisting of hydrogen, hydroxy, halogeno, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (1-6C)alkoxy, (3-6C)cycloalkoxy, (3-6C)cycloalkyl-(1-6C)alkoxy, carboxy, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, aminosulphonyl, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl and (3-6C)cycloalkylsulphonyl;

and wherein any of the  $R^a$ ,  $R^b$ ,  $R^c$  and/or  $R^d$  substituents on  $Q_a$  or  $Q_b$  defined hereinbefore which comprise a  $CH_2$  group attached to 2 carbon atoms or a  $CH_3$  group attached to a carbon atom may optionally bear on each said  $CH_2$  or  $CH_3$  group that include a methylene or methyl group may optionally be substituted on said methylene or methyl group with one or more substituents independently selected from the group consisting of hydroxy, cyano, amino, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

or a pharmaceutically-acceptable salt thereof.

**Claim 2** (currently amended): A compound of the Formula I according to ~~claim 1~~ wherein  $Q_a$  may optionally bear 1 or 2 substituents The compound or pharmaceutically acceptable salt of claim 1 in which  $R^a$  and  $R^b$  are each, independently of one another, selected from the group consisting of hydrogen, halogeno, (1-6C)alkyl and (1-6C)alkoxy; or a pharmaceutically acceptable salt thereof.

**Claim 3** (currently amended): A compound of the Formula I according to ~~claim 1~~ wherein  $Q_a$  may optionally bear 1 or 2 substituents The compound or pharmaceutically acceptable salt of claim 1 in which the  $R^c$  and  $R^d$  are each, independently of one another, selected from the group consisting of hydrogen, hydroxy, halogeno, (1-6C)alkyl and (1-6C)alkoxy; or a pharmaceutically acceptable salt thereof.

**Claims 4-6** (previously cancelled).

2 **Claim 7** (currently amended): A compound of the Formula I according to The compound or pharmaceutically acceptable salt of claim 1 or claim 2 wherein  $R_1$  and  $R_2$  are each independently of one another selected from the group consisting of hydrogen and (1-6C)alkyl; or a pharmaceutically acceptable salt thereof.

**Claim 8** (previously cancelled).

**Claim 9** (currently amended): A compound of the Formula I according to ~~claim 1~~ selected from the group consisting of:

*N*-cyclopropyl-4-methyl-3-[[4-(pyridine-2-ylmethoxy)benzoyl]amino} benzamide;

*N*-cyclopropyl-4-methyl-3-[[4-(pyridine-3-ylmethoxy)benzoyl]amino} benzamide;

*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-3-methoxy-4-(pyridin-2-ylmethoxy)benzamide;

*N*-cyclopropyl-4-methyl-3-[[3-methyl-4-(pyridin-2-ylmethoxy) benzoyl]amino} benzamide;



*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-3-fluoro-4-(pyridin-2-ylmethoxy)benzamide;  
*N*-cyclopropyl-4-methyl-3-{{3-(pyridin-2-ylmethoxy)benzoyl}amino}benzamide;  
 3-chloro-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-(pyridin-2-ylmethoxy)benzamide;  
*N*-cyclopropyl-3-{{4-[(4-methoxypyridin-2-yl)methoxy]benzoyl}amino}-4-methylbenzamide;  
*N*-cyclopropyl-4-methyl-3-{{4-(1-pyridin-2-ylethoxy)benzoyl}amino}benzamide;  
*N*-cyclopropyl-3-{{3-[(4-methoxypyridin-2-yl)methoxy]benzoyl}amino}-4-methylbenzamide;  
*N*-cyclopropyl-3-{{4-[[5-(hydroxymethyl)pyridine-2-yl]methoxy]benzoyl}amino}-4-methylbenzamide;  
*N*-cyclopropyl-3-{{4-[[5-(1-hydroxy-1-methylethyl)pyridin-2-yl]methoxy]benzoyl}amino}-4-methylbenzamide;  
*N*-cyclopropyl-3-{{4-{{5-[(isopropylamino)methyl]pyridin-2-yl}methoxy}benzoyl}amino}-4-methylbenzamide;  
*N*-cyclopropyl-3-{{4-{{5-[(dimethylamino)methyl]pyridin-2-yl}methoxy}benzoyl}amino}-4-methylbenzamide;  
 methyl 6-{{4-[[{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]phenoxy}methyl) nicotinate;  
*N*-cyclopropyl-3-{{4-{{5-[2-(dimethylamino)ethoxy]pyridin-2-yl}methoxy}benzoyl}amino}-4-methylbenzamide;  
*N*-cyclopropyl-3-{{4-[[5-(hydroxypyridin-2-yl)methoxy]benzoyl}amino}-4-methylbenzamide;  
 methyl 6-{{4-[[{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]phenoxy}methyl) pyridine-2-carboxylate;  
*N*-cyclopropyl-3-{{4-[[6-(hydroxymethyl)pyridin-2-yl]methoxy]benzoyl}amino}-4-methylbenzamide;  
*N*-cyclopropyl-3-{{4-[[6-(1-hydroxy-1-methylethyl)pyridin-2-yl]methoxy]benzoyl}amino}-4-methylbenzamide;  
*N*-cyclopropyl-3-{{4-[[6-{2-(diethylamino)ethoxy}methyl]pyridin-2-yl]methoxy]benzoyl}amino}-4-methylbenzamide;  
*N*-cyclopropyl-3-{{4-[[6-{2-(dimethylamino)ethoxy}methyl]pyridin-2-yl]methoxy]benzoyl}amino}-4-methylbenzamide;  
 3-{{4-[[6-bromopyridin-2-yl]methoxy]benzoyl}amino}-*N*-cyclopropyl-4-methylbenzamide;

*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-3,5-difluoro-4-(pyridin-2-ylmethoxy)benzamide;

*N*-cyclopropyl-4-methyl-3-({4-[(6-methylpyridin-2-yl)methoxy]benzoyl}amino)benzamide;

*N*-cyclopropyl-4-methyl-3-({4-[(3-methylpyridin-2-yl)methoxy]benzoyl}amino)benzamide;

*N*-cyclopropyl-3-{{4-{{6-[(2-methoxyethyl)amino]pyridin-2-yl}methoxy}benzoyl}amino)-4-methylbenzamide; and

*N*-cyclopropyl-3-{{4-{{6-{{2-(dimethylamino)ethyl}amino}pyridin-2-yl}methoxy}benzoyl}amino)-4-methylbenzamide;

or a and pharmaceutically-acceptable salt salts thereof.

**Claim 10** (cancelled herein).

**Claim 11** (currently amended): A pharmaceutical composition ~~which comprises a compound of the Formula I as claimed in any one of claims 1, 2 and 9, or a pharmaceutically acceptable salt thereof, in association with~~ comprising a compound or pharmaceutically acceptable salt according to any one of claims 1, 2, 3, 7, 9, 17, 18, 19, 20, 21 and 22 and a pharmaceutically-acceptable diluent or carrier.

**Claims 12-15** (previously cancelled).

**Claim 16** (withdrawn and currently amended): A method for ~~the treatment of rheumatoid arthritis, osteoarthritis, asthma, chronic obstructive pulmonary disease, inflammatory bowel disease, multiple sclerosis, AIDS, septic shock, congestive heart failure, ischaemic heart disease or psoriasis in a warm-blooded animal in need thereof~~ treating arthritis comprising administering to said animal a subject suffering from arthritis an effective amount of a compound of the Formula I as claimed in any one of claims 1, 2 and 9, or a pharmaceutically-acceptable salt thereof or pharmaceutically acceptable salt according to any one of claims 1, 2, 3, 7, 9, 17, 18, 19, 20, 21 and 22.

**Claim 17** (currently amended): ~~The compound~~ *N*-cyclopropyl-4-methyl-3-{{4-(pyridin-2-ylmethoxy)benzoyl}amino}benzamide, or a pharmaceutically-acceptable salt thereof.

**Claim 18** (currently amended): ~~The compound~~ *N*-cyclopropyl-4-methyl-3-{{4-(pyridin-3-ylmethoxy)benzoyl}amino}benzamide, or a pharmaceutically-acceptable salt thereof.

**Claim 19** (currently amended): ~~The compound~~ *N*-{5-(cyclopropylamino)carbonyl}-2-methylphenyl}-3-methoxy-4-(pyridin-2-ylmethoxy)benzamide, or a pharmaceutically-acceptable salt thereof.

**Claim 20** (currently amended): ~~The compound~~ *N*-cyclopropyl-4-methyl-3-{{3-methyl-4-(pyridin-2-ylmethoxy)benzoyl}amino}benzamide, or a pharmaceutically-acceptable salt thereof.

**Claim 21** (currently amended): ~~The compound~~ *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-3-fluoro-4-(pyridin-2-ylmethoxy)benzamide, or a pharmaceutically-acceptable salt thereof.

**Claim 22** (currently amended): ~~The compound~~ 3-chloro-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-(pyridin-2-ylmethoxy)benzamide, or a pharmaceutically-acceptable salt thereof.

**Claim 23** (new): A method of treating arthritis comprising administering to a subject in need there of an effective amount of a pharmaceutical composition according to **claim 16**.

**Claim 24** (new): A method of inhibiting a p38 kinase, comprising contacting a p38 kinase with a compound or pharmaceutically acceptable salt according to **any one of claims 1, 2, 3, 7, 9, 17, 18, 19, 20, 21 and 22**.

## REMARKS

Prior to entry of the instant Amendment, claims 1-3, 7, 9, 11 and 17-22 were pending and under consideration, with claims 10 and 16 being withdrawn from consideration as being drawn to non-elected inventions and pending rejoinder upon allowance of other claims. With this Amendment, pending claims 1-3, 7, 9, 11 and 17-22 and withdrawn claim 16 are being amended. Withdrawn claim 10 is being canceled. Thus after entry of this Amendment, claims 1-3, 7, 9, 11 and 17-24 are pending and under consideration. Claims 1-3, 7, 9, 11 and 17-22 remain rejected. The amendments of the claims and the rejections of record are discussed in more detail below.

### **I. The Amendments of the Claims**

With this Amendment, pending claims 1-3, 7, 9, 11 and 17-22 and withdrawn claim 16 are being amended and claims 23-24 are being newly added. None of the amended or new claims present new matter.

For example, claim 1 has been amended to replace the structural diagram of formula I with a new diagram that reflects the definitions of  $Q_a$  and  $Q_b$ . Claims 2-3, 7, 9, and 17-22 have been amended for grammatical clarity and conform their antecedent basis to amended claim 1. Claims 11 and 16 have been amended to multiply depend upon any one of claims 1-3, 7, 9 and 17-22. None of these amendments introduces new matter.

New claim 23 is directed to a method of treating arthritis that involves administering to a subject an effective amount of a pharmaceutical composition according of claim 16. This claim is supported by the disclosure at, for example, page 32, lines 15-19, 20-24 and lines 27-31.

New claim 24 is directed to a method of inhibiting a p38 kinase using a compound according to any of claims 1-3, 7, 9 and 17-22. This claim is supported by the disclosure at, for example, page 31, lines 5-8 and page 32, lines 2-14.

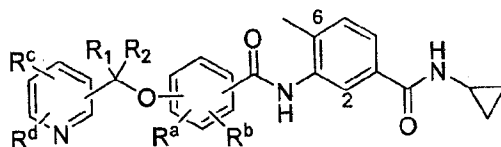
Since new claims 23 and 24 depend from pending claims, they should be eligible for rejoinder upon allowance of the claims from which they depend. Accordingly, entry is respectfully requested.

## II. Rejection of Claims 1-3, 7, 9, 11 and 17-22 Under 35 U.S.C. § 103(a)

The Office has maintained the rejection of claims 1-3, 7, 9, 11 and 17-22 as being allegedly obvious over WO 00/07980 to Brown *et al.* ("Brown *et al.*"). Applicant traverses the rejection on the grounds that the Office has failed to establish a *prima facie* case of obviousness and has ignored objective evidence of unexpected superior properties disclosed in the application.

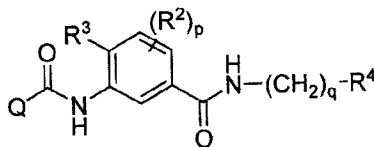
### A. The Office Has Failed To Establish *Prima Facie* Obviousness

Amended claim 1 is drawn to chemical compounds and pharmaceutical salts defined by the following structural formula:

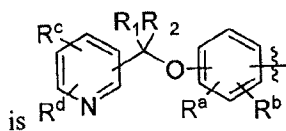


where the  $R_1$ ,  $R_2$ ,  $R^a$ ,  $R^b$ ,  $R^c$  and  $R^d$  substituents are as defined in claim 1. The claimed compounds inhibit p38 kinase and are useful for myriad purposes related to this inhibitory activity.

Brown *et al.* discloses p38 kinase inhibitory compounds and salts defined by the following structural diagram (arranged in the same orientation as structural formula I of the instant amended claim 1):



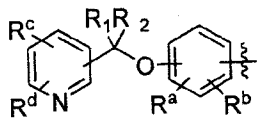
where the various  $p$ ,  $q$ ,  $Q$ ,  $R^3$  and  $R^4$  substituents are defined in the reference. As can be seen from these structural diagrams, amended claim 1 is directed to a subgenus of the compounds disclosed by Brown *et al.*, specifically, the subgenus of compounds in which  $p$  is 0,  $q$  is 0,  $R^3$  is methyl,  $R^4$  is cyclopropyl and  $Q$

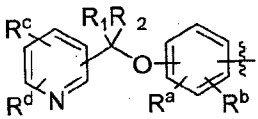


is  $R^d$ . According to the Office, this subgenus is rendered *prima facie* obvious by Brown *et al.* because Brown *et al.* include "cycloalkyl" as one of many possible alternatives for

substituent  $R^4$  and phenyl substituted with 1, 2 or 3 substituents selected from an extensive list of alternatives, one of which is pyridyl-(1-6C)alkoxy, for substituent Q (see Brown *et al.* at page 23, line 22 through page 24, line 6, with pyridyl-(1-6C)alkoxy appearing at page 23, line 30).<sup>1</sup> From these listed alternatives, the Office concludes that “[i]n view of the art as a whole, amides of formula (I) with pyridyl as the heteroaryl substituent of the alkoxy would have been obvious to one of ordinary skill in the art.” Applicant disagrees.

As noted, the instantly claimed compounds are directed to a subgenus of compounds within those generically taught by Brown *et al.* that are characterized by a specific combination of features:

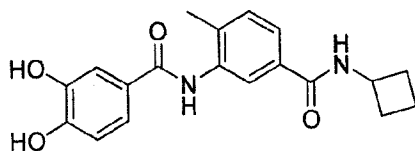
compounds in which  $q$  is 0,  $R^4$  is cyclopropyl and Q is . This specific subgenus is neither taught nor suggested by Brown *et al.*, and the Office has failed to provide any reasoning whatsoever as to why or how the “art as a whole” renders this subgenus *prima facie* obvious. To the extent that Brown *et al.* teach preferred subgenres of compounds, none of them include compounds in which substituent Q is a phenyl substituted with a heteroaryl such as a pyridyl, let alone with the specific

 substituent presently claimed. Moreover, with the exception of the compounds disclosed in Examples 9 and 11 of Brown *et al.*, in all of the exemplary compounds and subgenres taught by Brown *et al.*, substituent  $R^4$  is a substituted phenyl. In the instantly claimed compounds, the  $R^4$  substituent is cyclopropyl.

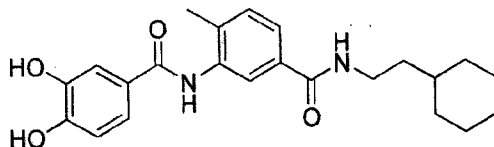
Two compounds in Brown *et al.* include a cycloalkyl at position  $R^4$ : the compounds of Examples 9 and 11. These compounds are illustrated below:

<sup>1</sup> The Office also relies upon page 5, lines 14-15 of Brown *et al.*, which provides heteroaryl-(1-6C)alkoxy as one of many possible alternative substituents when Q is phenyl or heteroaryl, and page 30, lines 10-11, which is irrelevant as it pertains to the situation when  $R^4$  is a substituted phenyl. In the compounds of the instant claim 1, the  $R^4$  position is cyclopropyl.

Ex 9:

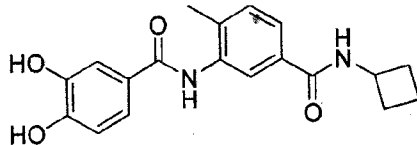


Ex 11:

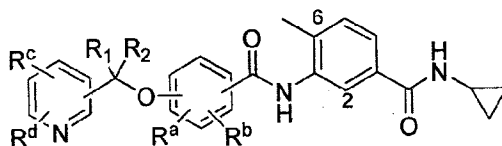


To the extent the Office is relying upon these compounds as being “closely structurally related differing by one next adjacent homologue in a substituent,” Office Action at page 3, the Office is mistaken. While the cyclobutyl substituent of the compound of Brown *et al.* Example 9 may be a homolog of the cyclopropyl substituent of the instantly claimed compounds, the compound of Example 9 does not bear structural similarity to the instantly claimed compounds, which include three aromatic rings. The above-illustrated compounds include only two. Thus, while the Office asserts that there is close structural similarity between the compounds disclosed in Brown *et al.* and the instantly claimed compounds, the Office has failed to identify such compounds. The compound of Example 9 is not so structurally similar to the instantly claimed compounds as to render the instantly claimed compounds *prima facie* obvious. The Office implies the instantly claimed compounds are mere structural homologues of the compound of Brown *et al.* Example 9. As illustrated by the structural diagram below, they are not:

Ex. 9



Claim 1



Nor has the Office explained why it would have been obvious to one of skill in the art to select for substituent Q of Brown *et al.* a phenyl substituted with a heteroaryl-(1-6C)alkoxy, where this particular substituent is only one amongst numerous possibilities, and then further select an optionally di-

substituted methyleneoxy and an optionally di-substituted pyridyl as the (1-6C)alkoxy and heteroaryl groups, respectively, when none of the specifically exemplified compounds or subgenres of Brown *et al.* include phenyls substituted with heteroaryl (1-6C)alkoxy groups for substituent Q.

The Federal Circuit has consistently held that a disclosure of a generic formula that may encompass a claimed compound or subgenus does not, without more, render the claimed compound or subgenus obvious. For example, in *In re Baird*<sup>2</sup>, the Federal Circuit found non-obvious claims to a toner composition including a bisphenol A polyester in light of a prior art patent teaching a toner composition including a generic polymeric esterification product encompassing a bisphenol A polyester. In so holding, the Court noted that the generic formula disclosed in the prior art reference included a large number of variables, and while it encompassed the claimed bisphenol A polyester when specific variables were chosen, there was nothing in the prior art reference suggesting that one should select such variables:

In the instant case, the generic diphenol formula disclosed in Knapp contains a large number of variables, and we estimate that it encompasses more than 100 million different diphenols, only one of which is bisphenol A. While the Knapp formula unquestionably encompasses bisphenol A when specific variables are chosen, there is nothing in the disclosure of Knapp suggesting that one should select such variables.

*In re Baird*, 29 USPQ2d at 1552. In fact, the Court further noted that the prior art reference, by focusing on more complex bisphenols, tended to teach away from the claimed bisphenol A polyester, explicitly noting that none of the disclosed bisphenols suggested bisphenol A:

Indeed, Knapp appears to teach away from the selection of bisphenol A by focusing on more complex diphenols, including 2,2-bis(4-beta-hydroxyethoxyphenyl) propane, 2,2-bis(4-hydroxypropoxyphenyl) propane, and 2,2-bis(4-hydroxyisopropoxyphenyl)propane. Col. 4, lines 51-64. Knapp teaches that in preferred diphenols, R has 2 to 4 carbon atoms and R' and R" have 3 to 4 carbon atoms, and in "optimum" diphenols, R is an isopropylidene radical, R' and R" are selected from the group consisting of propylene and butylene radicals, and n is one. Col. 4, lines 38-47. Knapp further states that the diphenol in the preferred polyester material is 2,2-bis(4-hydroxyisopropoxy phenyl)propane. Col. 5, lines 36-38. Fifteen typical diphenols are recited. None of them, or any of the other preferred phenols recited above, is or suggests bisphenol A.

"[A] reference must be considered not only for what it expressly teaches, but also for what it fairly suggests." *In re Burckel*, 592 F.2d 1175, 1179, 201 USPQ 67, 70 (CCPA 1979). Given the vast number of diphenols encompassed by the generic diphenol formula in Knapp, and the fact that the diphenols that Knapp specifically discloses to be

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<sup>2</sup> *In re Baird*, 29 USPQ2d 1550 (Fed. Cir. 1994)



“typical,” “preferred,” and “optimum” are different from and more complex than bisphenol A, we conclude that Knapp does not teach or fairly suggest the selection of bisphenol A. See *In re Bell*, 991 F.2d 781, 26 USPQ2d 1529 (Fed.Cir. 1993) (DNA sequence would not have been obvious in view of prior art reference suggesting a nearly infinite number of possibilities and failing to suggest why among all those possibilities one would seek the claimed sequence). A disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a preference leading away from the claimed compounds.

*In re Baird*, 29 USPQ2d at 1552.

The instant situation is similar. The generic compounds disclosed by Brown *et al.* include a large number of variables. While the specific combination of variables recited in instant claim 1 is encompassed by the disclosure of Brown *et al.* when specific variables are chosen, there is nothing in the Brown *et al.* reference to suggest the selection. And, by virtue of focusing on specific compounds that are different from those presently claimed, Brown *et al.* actually teaches away from the subgenus claimed in amended claim 1.

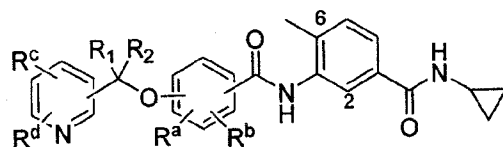
Accordingly, for the reasons discussed above, Brown *et al.* does not render amended independent claim 1 *prima facie* obvious. Since claims 2, 3, 7, 9, 11 and 17-24 ultimately depend from claim 1, they are also not rendered *prima facie* obvious for the same reasons.<sup>3</sup> Accordingly, the rejection of claims 1-3, 7, 9, 11 and 17-22 under 35 U.S.C. § 103(a) should be withdrawn.

#### **B. The Claimed Compounds Exhibit Unexpectedly Superior Inhibitory Activity**

The Office has also ignored objective evidence of unexpected superior inhibitory properties disclosed in the application. As noted above, the compounds of amended claim 1, and all pending claims in the application, include a cyclopropyl amide substituent at the 3-position of the central 6-methylphenyl core, illustrated below:

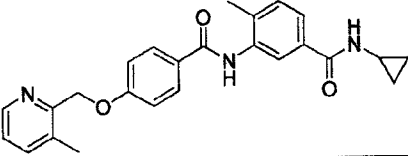
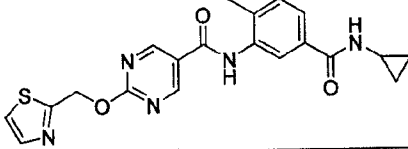
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<sup>3</sup> It is noted that claims 9 and 17-22 are directed to specific compounds. The Office has not supplied any reasoning whatsoever as to why Brown *et al.* obviate these claims. It is incumbent upon the Office to do so. Since no reasoning was supplied as to these claims, the rejection is improper and should be withdrawn for this additional reason.



Compounds including a cyclopropyl amide group at this position exhibit orders of magnitude greater inhibitory activity than compounds containing a cyclobutyl amide group at this position. These comparative data are presented at page 29 of the application, which provides p38 inhibitory for various compounds disclosed in the instant application (Compounds 5[ac], 5[e], 5[y], 5[z], 8 and 23[a]) as compared to "Comparator Compound X," which as noted at page 3 of the instant application is *N*-cyclobutyl-3-(3,4-dimethoxy benzamide)-4-methylbenzamide (*see* lines 9-12). This is the compound of Example 9 of Brown *et al.*, and discussed above. For the convenience of the Office, the table is reproduced below, including the structures of the compounds tested:

| Example      | Structure | P38a (μM) | Human Whole Blood (μM) |
|--------------|-----------|-----------|------------------------|
| Comparator X |           | 4.4       | >10                    |
| 5[ac]        |           | 0.007     | 0.07                   |
| 5[e]         |           | 0.01      | 0.52                   |
| 5[y]         |           | 0.006     | 0.14                   |
| 5[z]         |           | 0.007     | 0.30                   |

| Example | Structure   | P38a ( $\mu$ M) | Human Whole Blood ( $\mu$ M) |
|---------|---|-----------------|------------------------------|
| 8       |  | 0.059           | 1.8                          |
| 23[a]   |  | 0.17            | 1.7                          |

As can be seen from the data, compounds including the cyclopropyl amide group at the C3 position are several orders of magnitude more active in both *in vitro* and whole blood assays than comparator compound X, which includes a cyclobutylamide substituent at the C3 position. The unexpectedly superior activity is observed with compounds having various different substituents at the C1 position, including compounds having pyridylmethoxyphenyl amide substituents at this position, as presently claimed (*see, e.g.*, compound 5[y], recited in instant claim 21, and compound 8, recited in instant claim 9).

These data evidence that the full range of compounds disclosed in the instant application, and in particular the subgenus presently claimed, exhibit unexpectedly superior p38 inhibitory properties as compared to p38 inhibitory compounds bearing a cyclobutylamide substituent at the C3 position of the 6-methylphenyl ring illustrated in amended claim 1. The increased p38 inhibitory activity observed with compounds bearing a cyclopropylamide group at this position could not have been predicted. Accordingly, claims 1-3, 7, 9, 11 and 17-24 are non-obvious over the Brown *et al.* reference for this additional reason.

Accordingly, even if Brown *et al.* rendered instant claim 1 *prima facie* obvious, which it does not, the claims would still be non-obvious due to the unexpectedly superior inhibitory properties of the claimed compounds. Since claims 2, 3, 7, 9, 11 and 17-24 all ultimately depend from amended claim 1, they are likewise non-obvious for the same reasons. Accordingly, Applicant requests that the rejection of claims 1-3, 7, 9, 11 and 17-22 under 35 U.S.C. § 103(a) as being obvious over Brown *et al.* be withdrawn.

**Conclusion**

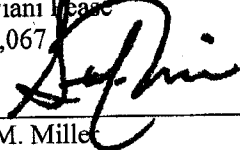
All pending claims are believed to satisfy the criteria for patentability and are believed to be in condition for allowance. An early indication of the same is therefore kindly requested.

The Director is authorized to charge the additional claims fees of **\$1,572.00** due in connection with this Amendment to Dechert LLP Deposit Account No. **50-2778** (Order No. **383299-336US (107322)**). The Director is also authorized to charge any additional fees that may be required to this same Deposit Account number.

Respectfully submitted,

Date: November 2, 2010

**DECHERT LLP**  
**Customer No. 37509**  
Tel: 650.813.4800  
Fax: 650.813.4848

ANN M. CAVIANI PEASE  
Ann M. Caviani Pease  
Reg. No. 42,067  
By:   
Stefan M. Miller  
Reg. No. 57,623

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

|             |  |                   |                       |
|-------------|--|-------------------|-----------------------|
| Applicant:  | Brown <i>et al.</i>  | Docket No:        | 383299-336US (107322) |
| Serial No.: | 10/581,305   | Confirmation No.: | 8437                  |
| Filed:      | October 12, 2006   | Group Art Unit:   | 1625                  |
| For:        | AMIDE DERIVATIVES BEARING A<br>CYCLOPROPYLAMINOACARBONYL<br>SUBSTITUENT USEFUL AS CYTOKINE<br>INHIBITORS | Examiner:         | COVINGTON, Raymond K  |

NOTICE OF APPEAL FROM THE EXAMINER TO THE  
BOARD OF PATENT APPEALS AND INTERFERENCES UNDER 37 CFR §41.31

**VIA EFS-WEB**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450

Sir:


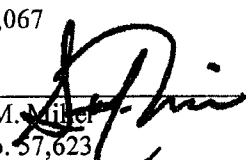
Applicant hereby appeals to the Board of Patent Appeals and Interferences from the last decision of the Examiner, mailed August 3, 2010 in the above-captioned application, finally rejecting the claims of the above-referenced application. The fee for the Notice of Appeal pursuant to 37 CFR § 41.20(b)(1) is \$540. Applicant is not claiming small entity status.

The Director is authorized to charge the fees specified above to **Dechert LLP Deposit Account No. 50-2778 (Order No. 383299-336US (107322))**. The Director is also authorized to charge any deficiencies, or credit any overpayment, in the fees specified to **Dechert LLP Deposit Account No. 50-2778 (Order No. 383299-336US (107322))**. Please direct any inquiries in connection with the above referenced application to the undersigned at 650.813.4800.

Respectfully submitted,

Date: November 2, 2010

**DECHERT LLP**  
Customer No. 37509  
Tel: 650.813.4800  
Fax: 650.813.4848

  
Ann M. Caviani Pease  
Reg. No. 42,067  
By:   
Stefan M. Miller  
Reg. No. 57,623

## Electronic Patent Application Fee Transmittal

|   |   |                 |               |                             |
|---|---|-----------------|---------------|-----------------------------|
| <b>Application Number:</b>                              | 10581305  |                 |               |                             |
| <b>Filing Date:</b>                                     | 12-Oct-2006   |                 |               |                             |
| <b>Title of Invention:</b>                              | Amide derivatives bearing a cyclopropylaminoacarbonyl substituent useful as cytokine inhibitors |                 |               |                             |
| <b>First Named Inventor/Applicant Name:</b>             | Dearg Sutherland Brown  |                 |               |                             |
| <b>Filer:</b>   | Stefan Michael Miller/Sherrice Breland  |                 |               |                             |
| <b>Attorney Docket Number:</b>                          | 383299-336US (107322)   |                 |               |                             |
| Filed as Large Entity                                   |   |                 |               |                             |
| <b>U.S. National Stage under 35 USC 371 Filing Fees</b> |   |                 |               |                             |
| <b>Description</b>                                      | <b>Fee Code</b>   | <b>Quantity</b> | <b>Amount</b> | <b>Sub-Total in USD(\$)</b> |
| <b>Basic Filing:</b>                                    |   |                 |               |                             |
| <b>Pages:</b>   |   |                 |               |                             |
| <b>Claims:</b>  |   |                 |               |                             |
| Claims in excess of 20                                  | 1615  | 26              | 52            | 1352                        |
| Independent claims in excess of 3                       | 1614  | 1               | 220           | 220                         |
| <b>Miscellaneous-Filing:</b>                            |   |                 |               |                             |
| <b>Petition:</b>  |   |                 |               |                             |
| <b>Patent-Appeals-and-Interference:</b>                 |   |                 |               |                             |
| Notice of appeal  | 1401  | 1               | 540           | 540                         |

| Description                       | Fee Code | Quantity | Amount | Sub-Total in USD(\$) |
|-----------------------------------|----------|----------|--------|----------------------|
| Post-Allowance-and-Post-Issuance: |          |          |        |                      |
| Extension-of-Time:                |          |          |        |                      |
| Miscellaneous:                    |          |          |        |                      |
| Total in USD (\$)                 |          |          |        | 2112                 |

## Electronic Acknowledgement Receipt

|   |   |
|---|---|
| <b>EFS ID:</b>                              | 8754201   |
| <b>Application Number:</b>                  | 10581305  |
| <b>International Application Number:</b>    |   |
| <b>Confirmation Number:</b>                 | 8437  |
| <b>Title of Invention:</b>                  | Amide derivatives bearing a cyclopropylaminoacarbonyl substituent useful as cytokine inhibitors |
| <b>First Named Inventor/Applicant Name:</b> | Dearg Sutherland Brown  |
| <b>Customer Number:</b>                     | 37509   |
| <b>Filer:</b>                               | Stefan Michael Miller/Sherrice Breland  |
| <b>Filer Authorized By:</b>                 | Stefan Michael Miller   |
| <b>Attorney Docket Number:</b>              | 383299-336US (107322)   |
| <b>Receipt Date:</b>                        | 02-NOV-2010   |
| <b>Filing Date:</b>                         | 12-OCT-2006   |
| <b>Time Stamp:</b>                          | 16:58:07  |
| <b>Application Type:</b>                    | U.S. National Stage under 35 USC 371  |

### Payment information:

|   |                 |
|---|-----------------|
| Submitted with Payment  | yes             |
| Payment Type  | Deposit Account |
| Payment was successfully received in RAM  | \$2112          |
| RAM confirmation Number   | 3443            |
| Deposit Account   | 502778          |
| Authorized User   |                 |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:<br>Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges) |                 |



**File Listing:**

| Document Number | Document Description | File Name                                  | File Size(Bytes)/<br>Message Digest      | Multi Part /.zip | Pages (if appl.) |
|-----------------|----------------------|--|--|------------------|------------------|
| 1               | Transmittal Letter   | Flexion336US-<br>Amendment_Transmittal.pdf | 144089                                   | no               | 2                |
|                 |                      |  | 55038888ac0fcab8a491a78a5918793b1c6887b1 |                  |                  |

**Warnings:****Information:**

|   |                       |   |  |    |    |
|---|-----------------------|---|--|----|----|
| 2 | Amendment After Final | Flexion336US-<br>Amendment_and_Response_t<br>o_Final_OA.pdf | 1467313                                | no | 15 |
|   |                       |   | 9039186f0742e30ed7fac5e51a3904c2a1a314 |    |    |

**Warnings:****Information:**

|   |                        |                                       |  |    |   |
|---|------------------------|---------------------------------------|--|----|---|
| 3 | Notice of Appeal Filed | Flexion336US-<br>Notice_Of_Appeal.pdf | 96996                                    | no | 1 |
|   |                        |                                       | 7d23646a9263eaa800d249aaf853e4ee29577488 |    |   |

**Warnings:****Information:**

|   |                         |              |  |    |   |
|---|-------------------------|--------------|--|----|---|
| 4 | Fee Worksheet (PTO-875) | fee-info.pdf | 35404                                    | no | 2 |
|   |                         |              | bbe3eed5fe0350d07a2d4610caf86a430a5923b0 |    |   |

**Warnings:****Information:****Total Files Size (in bytes):**

1743802

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

|             |  |                   |                       |
|-------------|--|-------------------|-----------------------|
| Applicant:  | Brown <i>et al.</i>  | Docket No:        | 383299-336US (107322) |
| Serial No.: | 10/581,305   | Confirmation No.: | 8437                  |
| Filed:      | October 12, 2006   | Group Art Unit:   | 1625                  |
| For:        | AMIDE DERIVATIVES BEARING A<br>CYCLOPROPYLAMINOACARBONYL<br>SUBSTITUENT USEFUL AS CYTOKINE<br>INHIBITORS | Examiner:         | COVINGTON, Raymond K  |

## AMENDMENT TRANSMITTAL

### VIA EFS-WEB

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir :

Transmitted herewith are the following documents in the above-referenced application:

### I. ENCLOSURES

- ☒ Response and Amendment Under 37 CFR § 1.116 (15 pages); and
- ☒ Notice of Appeal from the Examiner to the Board of Patent Appeals and Interferences under 37 CFR § 41.31 (1 page)

### II. FEE FOR CLAIMS

- ☒ The fee for claims (37 CFR 1.16(b)-(d)) has been calculated as shown below:

| (Col. 1)   |    | (Col. 2)                              |    | (Col. 3)         |    | SMALL ENTITY        | OR            | OTHER THAN A<br>SMALL ENTITY |                     |
|--|----|---------------------------------------|----|------------------|----|---------------------|---------------|------------------------------|---------------------|
| Claims<br>Remaining<br>After<br>Amendment                          |    | Highest No.<br>Previously<br>Paid For |    | Present<br>Extra |    | Rate                | Addit.<br>Fee | Rate                         | Addit.<br>Fee       |
| Total  | 46 | Minus                                 | 20 | =                | 26 | x26=                | \$0           | x52=                         | \$1,352.00          |
| Indep.   | 8  | Minus                                 | 7  | =                | 1  | x110=               | \$0           | x220=                        | \$220               |
| <input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEP. CLAIM |    |                                       |    |                  |    | +195=               | \$0           | x390=                        | \$0                 |
|  |    |                                       |    |                  |    | TOTAL<br>ADDIT. FEE | \$0           | OR                           | TOTAL<br>ADDIT. FEE |
|  |    |                                       |    |                  |    |                     |               |                              | \$1,572.00          |

- ☐ No additional fee for claims required.
- ☒ Total additional fee for claims required **\$ 1,572.00**

**III. FEE PAYMENT**

- ☒ The Director is authorized to charge the fees specified above to the **Dechert LLP Deposit Account No. 50-2778 (Order No. 383299-336US (107322))**:
- ☒ Additional Claim Fees in the amount of **\$ 1,572.00**
- ☒ Notice of Appeal Fee in the amount of **\$ 540.00**
- ☒ Total amount due: **\$2,112.00**

**IV. FEE DEFICIENCY**

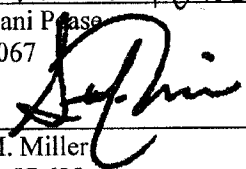
- ☒ The Director is authorized to charge any deficiencies in the fees specified to the **Dechert LLP Deposit Account No. 50-2778 (Order No. 383299-336US (107322))**.
- ☒ The Director is authorized to credit any overpayment in the fees specified to the **Dechert LLP Deposit Account No. 50-2778 (Order No. 383299-336US (107322))**.

Respectfully submitted,

Date: November 2, 2010

**DECHERT LLP**  
**Customer No. 37509**  
Tel: 650.813.4800  
Fax: 650.813.4848

ANN M. CAVIANI PEASE  
Ann M. Caviani Pease  
Reg. No. 42,067

By:   
Stefan M. Miller  
Reg. No. 57,623

# **Exhibit B**



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**Total Assignments: 1****Patent #:** [Z943726](#)**Issue Dt:** 05/17/2011**Application #:** 10581305**Filing Dt:** 10/12/2006**Publication #:** [20070135440](#)**Pub Dt:** 06/14/2007**Inventors:** Dearg Sutherland Brown, John Graham Cumming, Ian Alun Nash**Title:** AMIDE DERIVATIVES BEARING A CYCLOPROPYLAMINOACARBONYL SUBSTITUENT USEFUL AS CYTOKINE INHIBITORS**Assignment: 1****Reel/Frame:** [Q18127/Q351](#)**Recorded:** 07/25/2006**Pages:** 3**Conveyance:** ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).**Assignors:** [BROWN, DEARG SUTHERLAND](#)**Exec Dt:** 05/24/2006[CUMMING, JOHN GRAHAM](#)**Exec Dt:** 05/24/2006[NASH, IAN ALUN](#)**Exec Dt:** 05/24/2006**Assignee:** [ASTRAZENECA AB](#)

SE-151 85 SODERTALJE, SWEDEN

**Correspondent:** MORGAN LEWIS & BOCKIUS LLP

1111 PENNSYLVANIA AVENUE NW

WASHINGTON, DC 20004

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